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UNDERSTANDING THE DISEASE

Critical care management of infectious meningitis and encephalitis

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Central nervous system (CNS) infections represent 2.9% of the infections encountered in the intensive care unit (ICU) [1]. Among them, infectious meningitis and encephalitis, regardless of their community or healthcare-associated origin, often have dramatic consequences, including permanent brain injury and mortality. Due to the potential severity of presentation and the acute risk of mortality, many of these patients are admitted to the ICU. Their management requires a thorough understanding of not only epidemiology and diagnostic workup, but also of antimicrobial and adjunctive treatments.

Epidemiology

Acute bacterial meningitis

The worldwide incidence of acute bacterial meningitis is highly variable depending on the region, ranging from 207.4 (95% UI 183.9–233.9) per 100,000 in South Sudan to as low as 0.5 (0.4–0.7) per 100,000 in Australia [2]. Mortality is high, ranging from 17 to 40%, depending on causative pathogen and country income status. The global number of meningitis-related deaths has decreased by 21% from 1990 to 2016 [2], mainly in children younger than 5 years. For older patients, the number of deaths worldwide reduced only by 2.7% from 1990 to 2013 [3].

In a pooled analysis of studies from European countries, 53% of acute bacterial meningitis cases in adults were due to *Streptococcus (S.) pneumoniae*, 27% to *Neisseria* (*N.) meningitidis* and 13% caused *by Listeria (L.) monocytogenes* [4]. Five serogroups of meningococci are responsible for most cases of invasive meningococcal disease—A, B, C, W135 and Y. Common risk factors for listeriosis include exposure to contaminated food, older age (>65 years), and immunocompromised states [5]. *Haemophilus (H.). influenzae* and *Staphylococcus (S.) aureus* comprise 1–2% of cases in adults, usually in specific clinical circumstances, such as sinusitis and endocarditis, respectively [4].

The current epidemiology of community-acquired bacterial meningitis cannot be understood without taking into account the impact of vaccination [6]. Over the past decades, large-scale immunization programs against *H. influenzae type b*, *N. Meningitidis serogroups A, C, W and Y* and against some serotypes of *S. Pneumoniae* have led to stark reductions in their incidence in vaccinated, but also in unvaccinated populations [7]. From Europe to Africa, the introduction of specific anti-meningococcal vaccines played an important role in reducing the incidence of the disease, such that *N. Meningitidis* is no longer the leading global cause of meningitis-associated mortality [2]. In the Netherlands, the incidence dropped from 4.5 to 0.6 cases per 100,000 people after vaccination in 2002 against serogroup C [8]. Currently, meningococcal meningitis is predominantly caused by serogroup B, and mostly found in adolescents, but this might change now that the first serogroup B vaccine has been introduced [9]. In addition to its established effectiveness in children, pneumococcal vaccination has recently been evaluated in a large placebo-controlled trial of elderly adults (more than 65 years of age) and was found to be effective in preventing vaccine-type pneumococcal pneumonia and invasive pneumococcal disease [10]. Routine vaccination, through selective pressure, may lead to serotype replacement, especially in the case of *S. pneumoniae* [11]. Nevertheless, the predominant effect remains a net reduction of invasive pneumococcal disease [12].

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Among survivors, long-term disability plays a significant role and has been described in up to half of patients [8, 13]. *S. pneumoniae*, the main etiologic pathogen in the adult, also caused the largest number of years of life lived with disabilities [2]. Pneumococcal etiology has an independent association with poor outcome, together with other known risk factors such as age, systemic compromise, and reduced level of consciousness. The prospective multicenter PNEUMOREA cohort study reported a mortality rate of 33% (51/156) at 3 months after ICU admission in patients with pneumococcal meningitis, with neurologic sequelae observed in 34% of survivors [14].

Acute meningoencephalitis

Viral meningoencephalitis is an inflammation of the meninges and brain parenchyma caused by the infection of a neurotropic virus [15]. Data from population-based cohort studies conducted in high-income countries suggest that the *herpes simplex virus (HSV)* accounts for 22% of etiologies in immunocompetent adults [16]. *Enterovirus* is a frequent cause of encephalitis in infants and children, but not in the adult population. Arboviruses occur seasonally and according to specific geographical regions. West Nile virus, for example, is considered endemic in the USA. Other specific causative pathogens, such as Zika or Dengue, should be suspected during outbreaks in determined regions of the world. In a recent outbreak of Zika infection in Brazil, a series of 40 patients with neurological complications reported 18% of those with encephalitis [17]. Measles or mumps can be observed in unvaccinated patients.

Varicella-zoster virus (VZV) is the first etiology identified in immunocompromised patients [16]. *HSV* encephalitis in these patients may present atypically and is associated with poorer outcomes [18, 19]. Other viruses in immunocompromised population include *cytomegalovirus (CMV), human herpesvirus (HHV)-6 and -7* as well as *John Cunningham-virus (JCV)* [20].

Non-viral causes of acute encephalitis include *Mycobacterium tuberculosis*, which may account for 5% of etiologies of acute meningoencephalitis [16]. Other non-viral causes should be suspected in specific situations such as immunodepression (toxoplasmosis, cryptococcosis) or travel to endemic regions (malaria).

Non-infectious immune-mediated encephalitis, such as acute disseminated encephalitis (ADEM) and other antibody-associated causes, might represent 20% of causes presenting to the hospital [21].

Healthcare-associated ventriculitis and meningitis

Infectious meningitis and/or encephalitis may also develop after breaches in meningeal integrity, caused by head trauma, invasive procedures, or external ventricular drains (EVD). In a study from Taiwan, 48% of meningitis cases were classified as hospital acquired [22] and in a multicentric epidemiological study from the USA, the incidence of meningitis caused by nosocomial pathogens was similar to that caused by *N. meningitidis* [23]. Etiologic agents and pathogenesis differ significantly from community-acquired infections. Common pathogens include *coagulase-negative staphylococci (CNS)*, *Staphylococcus (S.) aureus,* and Gram-negative bacilli (including *Enterobacteriaceae, Pseudomonas aeruginosa* and *Acinetobacter* species) [24]. In traumatic brain injury (TBI), the incidence of meningitis is estimated to be 1.4%, but may be higher in the presence of depressed cranial fractures, basilar skull fractures and sinus cavity exposure. Bacterial meningitis after elective craniotomy occurs in 0.8–1.5% of patients and has been reported both in high-income countries and lower-resource settings. Risk factors include CSF drainage, the presence of CSF leaks and steroid use [25, 26]. A major source of infection in neurosurgical and neurocritical care units are external ventricular drains (EVD). The incidence of EVD-associated ventriculitis is approximately 8% (range 0 to 22%), depending on diagnostic criteria and patient population [24, 27]. A recent multicentric study from Italy [28] reported that 11% of patients with EVDs had ventriculitis or meningitis, with an early peak after EVD placement and a rise of the rate of meningitis/ventriculitis with increased lengths of catheterization. A large meta-analysis of 35 studies [29] found a pooled incidence of 11.4 per 1000 ventricular catheter days (95% CI 9.3–13.5), with progressively lower rates of infection with catheters in place for less than 7 days (19.6/1000 catheter-days), 7–10 days (12.8/1000 catheter-days) and more than 10 days (8/1000 catheter-days). These findings suggest that the duration of catheterization is not the only culprit of EVD infections, and that a significant proportion of infections may originate from the insertion procedure. The SiLuDrain trial [30] is a recently published randomized controlled trial (RCT) evaluating the effect of a silver-impregnated lumbar drain on the development of meningitis. The rates found were 4.2% in the intervention arm and 16.7% in the control group, a difference that was not statistically significant due to small sample size. However, the high incidence of infections in the control group was striking and unexplained. Internal CSF shunts as a long-term treatment for hydrocephalus may get infected in 4%–17%, but most studies were performed in children. In adults, internal shunts are usually inserted after hemorrhagic stroke and infections mostly occur within 1 month of the procedure [31], presumably due to colonization at the time of surgical insertion.

The epidemiology of infectious meningoencephalitis is summarized in Table 1.

Diagnostic workup

Clinical signs and symptoms

Infectious meningitis and encephalitis are medical emergencies, and early recognition and treatment are essential. The 'classic triad' of meningitis (neck stiffness, fever, and headache is present in less than 50% of cases and has low sensitivity [32]. Indeed, common symptoms of meningeal irritation (neck stiffness, the Kernig sign and the Brudzinski sign) do not accurately identify patients with meningitis [33]. Involvement of brain parenchyma due to direct inflammation or intracranial complications is responsible for changes in mental status, seizures and/or focal signs. Almost all meningitis patients present with at least two out of the four symptoms: neck stiffness, fever, altered mental status, or headache [8, 32].

The differential diagnosis can be complex, and non-infectious conditions such as tumors, toxic agents, autoimmune diseases, or paraneoplastic phenomena might have clinical features similar to meningoencephalitis. Intracerebral or epidural abscesses might also present with symptoms of meningoencephalitis.

Otogenic meningitis is a rare but serious complication of acute otitis media in children, associated with acute or chronic mastoiditis. A recent history of otitis media and in particular key symptoms such as persistent fever, headache, and purulent otorrhea should raise the level of suspicion [34].

Patients with meningococcal or pneumococcal meningitis often show signs of coexisting sepsis and may present with petechial skin rash. This clinical presentation may be obscured in severely immunocompromised patients, such as untreated HIV-positive individuals, or after bone marrow or solid organ transplantation [35].

Patients with viral encephalitis usually present with a rapid onset of encephalopathy, with a combination of various symptoms, including fever, focal signs, and generalized or focal seizures [15].

CSF examination

CSF examination is essential to confirm or rule out bacterial meningitis/encephalitis, and to identify other non-bacterial infections or immune-mediated diseases. A diagnostic tree is presented in Fig. 1. Physicians first need to verify whether a lumbar puncture is safe for the patient. Typical CSF findings that are assessed in the diagnosis meningitis/encephalitis are presented in Table 2. Gram staining allows for rapid identification of the causative organism in 60–90% of cases, while CSF culture remains the gold standard for the diagnosis of bacterial meningitis [36]. Latex agglutination testing in CSF has a widely varying sensitivity depending on the causative pathogen: 59–100% and 22–93% for *S. pneumoniae* and *N. meningitidis*, respectively. Blood cultures, collected before the start of antibiotic treatment, are positive in 66% of patients with bacterial meningitis [32] as well as in neurolisteriosis [5]. CSF polymerase chain reaction (PCR) is increasingly used, especially when antibiotic treatment has been initiated before the LP.

In patients with suspected viral encephalitis, no blood laboratory result can be used to guide the etiological diagnosis, but is nevertheless needed to establish a differential diagnosis [37]. CSF PCR for HSV, VZV, and enterovirus are imperative. Whether additional virologic evaluation for arboviruses is necessary, is based on the geographic region and season. Measles and mumps need to be excluded in unvaccinated patients [38]. In the absence of comorbidities and after reasonable exclusion of common infectious causes, non-infectious causes should systematically be considered, including ADEM [39] and antibody-associated encephalitis [40]).

The diagnostic workup in severely immunocompromised patients is more complex and has been covered more extensively in a recent review [35]. Importantly, only minimal CSF pleocytosis may be observed in these patients, making CSF Gram stain, PCR and cultures especially important. In addition, other pathogens should be systematically sought, including viruses (CMV, HHV6, HHV7, and JC virus), *Mycobacterium tuberculosis* and fungi [15]. *Mycobacterium tuberculosis* detection includes detection of acid-fast bacilli by microscopic examination (>2 ml CSF), real-time PCR, and mycobacterial cultures. CSF microscopic direct examination is rarely positive and real-time PCR has a negative predictive value of 84%, suggesting that a negative real-time PCR does not rule out tuberculous meningitis [37]. Blood and CSF IGRA (interferon gamma release assay) tests are currently not recommended. Other high-risk patients, in whom testing for tuberculosis is indicated, are the elderly (>75 years), and those coming from high incidence countries. Tuberculous meningitis in adult patients admitted to the ICU may be complicated by infarction, basilar arachnoiditis, hydrocephalus or abscess, as best detected on magnetic resonance (MR) scan [41]. Fungal meningitis should be systematically sought in patients with unexplained meningitis/encephalitis and in immunocompromised patients, with india ink stain direct examination, and cryptococcal antigen in both serum and CSF.

Recent data suggest that a multiplex PCR approach simultaneously detecting bacteria (*H. influenzae, N. meningitidis, L. monocytogenes, S. agalactiae, S. pneumoniae, H. influenzae*), viruses (HSV-1, HSV-2, CMV, VZV, HPV, HHV6, enterovirus) and yeast (Cryptococcus) has high sensitivity and specificity [42]. Antigen and immunochromatographic tests provide tools for rapid identification of the pathogen [43]. Routine microbiologic testing may not be sufficient to detect neuro-invasive pathogens

Table 1 Overview of the most common pathogens causing meningoencephalitis, and predisposing risk factors associated with these pathogens

Common pathogens	Comments and predisposing conditions
Bacterial meningitis	
Neisseria meningitidis	All ages affected; more common in younger patients Entry through nasopharynx; Usually no predisposing conditions
Streptococcus pneumoniae	All ages affected; more common in older adult patients Entry through nasopharynx, skull fractures, and contiguous or distant site of infection Predisposing conditions include HIV-infected individuals, pneumococcal bacteremia, fracture of cribriform plate, cochlear implants, and cerebrospinal fluid leaks from basilar skull fracture
Listeria monocytogenes	More common in older adults or neonates Entry through gastrointestinal tract or placenta Predisposing conditions include immunodeficiency—defects in cell-mediated immunity (i.e., glucocorticoids, transplantation), pregnancy, liver disease, alcoholism, malignancy
Coagulase-negative staphylococci	All ages affected; Entry through foreign body; Predisposed patients are those that underwent neurosurgery with foreign body (i.e., ventricular drains and shunts)
Staphylococcus aureus	All ages affected Entry through foreign body, neurosurgery or bacteremia Predisposition include endocarditis, neurosurgery, foreign body (i.e. ventricular drains and shunts), cellulitis with bacteremia
Gram-negative bacilli	More common in older adults, neonates, immunocompromised patients and all ages in hospitalized patients Predisposition include severity of systemic illness, neurosurgery, ventricular drains, disseminated strongyloidiasis
Haemophilus influenzae	Affects all ages Entry through nasopharynx and contiguous spread from local infection Predisposed patients are those with compromised humoral immunity and unvaccinated children
Viral encephalitis	
HSV 1 and 2	Affects all ages, immunocompetent individuals; Most common, 50 to 75% of identifiable cases No seasonal or geographic preferences
VZV	More common in immunocompromised adults or unvaccinated children Associated with viral reactivation, even in absence of skin lesions In children, most cases occur concurrently with chickenpox or in a post-infectious form
Enterovirus	Common cause among identifiable etiologies; common among children Fecal oral contamination May occur in outbreaks
Dengue, Zika	Varies upon geographic region and outbreak season, reflecting arboviral transmission
West Nile Virus	Depending upon geographic region. For example, it is considered endemic in the USA
EBV	More common in children and adolescents
CMV	More common in immunocompromised patients
Measles, mumps	In unvaccinated patients
Others	Evaluate geographic region, travel history, outbreak season, differential diagnosis (i.e,. autoimmune encephalitis)
Healthcare-associated meningitis and ventriculitis	
Staphylococcus aureus Coagulase-negative staphylococci (especially *Staphylococcus epidermidis*)	Penetrating traumatic brain injury, neurosurgery, ventricular and lumbar drains
Pseudomonas aeruginosa *Acinetobacter baumannii*	Neurosurgery with foreign body, especially ventricular drains
Propionibacterium acnes	Ventricular and lumbar drains
Streptococcus pneumoniae, *Haemophilus influenzae*, group A β-hemolytic streptococci	Basilar skull fracture

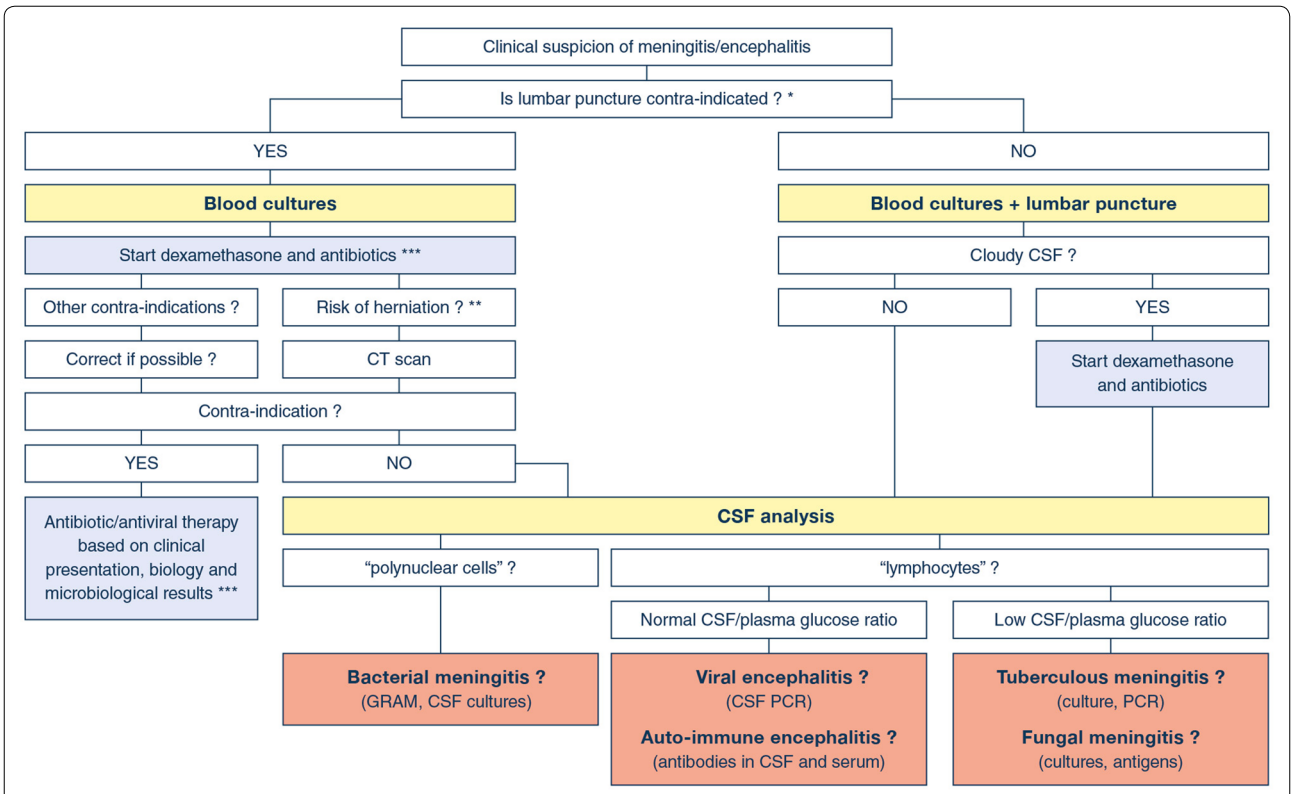

Fig. 1 Diagnostic algorithm in non-immunocompromised patients with suspected meningoencephalitis. *Contraindication to lumbar puncture includes severe coagulation abnormalities, hemodynamic instability, focal neurologic deficits (excluding cranial nerve palsies), new-onset seizures, severely altered mental status, and severely immunocompromised state (e.g., in organ transplant recipients and HIV-infected patients). **A space-occupying intracranial lesion or diffuse brain edema, which both cause a substantial brain shift, resulting in an increased risk of cerebral herniation. ***It is strongly recommended to start antibiotic therapy as soon as possible in acute bacterial meningitis patients. The time period until antibiotics are administered should not exceed 1 h. Whenever lumbar puncture is delayed, e.g., due to cranial CT, empiric treatment must be started immediately on clinical suspicion, even if the diagnosis has not been established. Intravenous aciclovir (10 mg/kg three times daily) should be started if the initial CSF and/or imaging findings suggest viral encephalitis, or within 6 h of admission if these results will not be available, or if the patient is very unwell or deteriorating

and metagenomic next-generation sequencing may provide actionable information in some cases [44].

When there is a known history of (potential) meningeal integrity breaches, such as craniofacial trauma, cranial surgery, or ventricular or lumbar shunts, it is important to consider healthcare-associated infections. Clinical symptoms may arise during hospitalization, but also late, up to months after hospital discharge. Implanted shunt systems may have a CSF sampling port of reservoir that can be punctured for diagnostics.

Imaging

In patients with bacterial meningitis, common intracranial complications detected on CT scan obtained at admission include cerebral ischemia (10%), diffuse cerebral edema (10%), hydrocephalus (3%) and empyema (1%) [45]. Brain MRI is the first-line imaging to perform in patients with suspected viral encephalitis, when it is feasible, and should include FLAIR, diffusion, T2*, and T1 sequences with and without gadolinium, as well as venous and arterial sequences [37]. Typical patterns of HSV encephalitis, such as bilateral temporal lobe involvement, may help to distinguish HSV from its mimics [46].

EEG

EEG may also add to clinical, diagnostic and prognostic information in patients with acute encephalitis [47], although the EEG abnormalities are often non-specific for the underlying cause.

Management

Antimicrobial treatment

Community-acquired meningitis

For community-acquired meningitis, prompt initiation of empirical antimicrobial treatment should not be delayed by the diagnostic process, and should be started within the first hour of presentation [4, 24], even if CSF

Table 2 Interpretation of cerebrospinal fluid (CSF) findings

	Normal	Bacterial	Viral	Tuberculous	Fungal
Opening pressure	6–20 cmH_2O	20–50 cmH_2O	6–30 cmH_2O	20–40 cmH_2O	20–100 cmH_2O
Colour	Clear	Cloudy	"Gin" clear	Cloudy/yellow	Clear/cloudy
Cells	< 5/mm^3	High-very high > 1000/mm^3	Slightly increased 10–1000/mm^3	Slightly increased 10–1000/mm^3	Normal-high 0–1000/mm^3
Differential	Lymphocytes	Neutrophils	Lymphocytes	Lymphocytes	Lymphocytes
CSF/blood glucose ratio	50–66%	Low < 40%	Normal	Low-very low < 30–40%	Normal-low
Protein level	< 0.45 g/l	> 1 g/l	0.5–1 g/l	1–5 g/l	0.5–5 g/l

Adapted from [37] and [57]

When performing a lumbar puncture for CSF sampling, the following should be observed:

The minimum amount of CSF sampled must be 120 drops (1 drop amounts to approximately 50 µL): 20 drops (1 mL) for biochemistry tests and 80–100 drops (4–5 mL) for microbiological and virological tests

Part of the CSF must be kept (at + 4 °C and then, if possible, at − 80 °C) for additional biological tests (including tuberculosis diagnostic test)

CSF glucose level must imperatively be combined with a concomitant blood glucose level test

examination is not possible. It should be maintained until CSF examination results are negative, or if suspicion of meningitis persists. Independent of severity at the time of ICU admission, delays in antibiotic treatment are predictive of mortality and unfavorable outcome [48]. The choice of antibiotic therapy for community-acquired (suspected) bacterial meningitis depends on the age of the patient, specific risk factors, and the local antibiotic resistance pattern of *S. Pneumoniae*. In patients between 18–50 years of age, cefotaxime or ceftriaxone should be adequate to cover for *S. Pneumoniae, H. Influenzae, and N. Meningitidis*. However, in areas with decreased susceptibility for these antibiotics, vancomycin or rifampicin [49] should be considered, even while there is currently no evidence for efficacy from human interventional clinical trials. *Listeria* coverage with amoxicillin, ampicillin, or penicillin G should be added in all patients > 50 years of age, or younger patients with risk factors (diabetes, impaired immunity, or cancer). Because listeriosis has been reported in patients < 50 years without risk factors as well, many local protocols have included Listeria coverage in all initial empiric regimens, regardless of age or risk. Community-acquired meningitis due to *E. coli* [50-52] should be considered in patients with risk factors such as a higher age, immune-suppression or concomitant other infections at admission (in particular, urinary tract infections). In most settings, *E. Coli* should be susceptible to standard empirical antibiotic regimen, although adding gentamicin might be considered [52, 53]. However, in regions where the prevalence of extended spectrum beta-lactamase (ESBL) or carbapenemase producing (CPO) *E. Coli* is significant, it could be an option to initiate treatment with carbapenem or colistin [54]. Once the causative organism has been identified, de-escalation is usually feasible. Standard duration of therapy is 7–10 days for *N. Meningitidis*, 10–14 days for *S. Pneumoniae* pneumococcal, and 21 days for *L. Monocytogenes*.

Adding dexamethasone together with the initial dose of antibiotics has been shown to decrease hearing loss and neurological sequelae in bacterial meningitis caused by *H. Influenzae* and *S. Pneumoniae*, and reduce mortality in pneumococcal meningitis, at least in high-income countries [55]. Whether adjuvant dexamethasone should be stopped when final microbiology demonstrates non-pneumococcal and non-haemophilus meningitis is controversial. A recent observational cohort in 120 adults found an association between dexamethasone use and delayed cerebral injury (DCI) [56], but the retrospective nature, small sample, and low event rate (only five patients developed DCI) in this study do not allow for any conclusion and certainly should not change practice.

In case of a brain or subdural abscess, or mastoiditis, consultation with a neurosurgeon or head and neck surgeon, and surgical drainage, will be necessary.

Acute viral encephalitis

If CSF or imaging is suggestive of viral encephalitis, aciclovir 10 mg/kg, three times per day (adapted to renal function) should be started immediately [57]. Even if CSF or imaging results cannot be obtained within 6 h of admission, or if the patient deteriorates before results become available, antiviral therapy should be initiated. Empirical aciclovir cannot be stopped until an alternative diagnosis of meningoencephalitis is confirmed, or viral encephalitis caused by an aciclovir-susceptible virus has been ruled out by (weekly repeated) negative LP, in the absence of radiological (MRI) signs of viral encephalitis. If HSV encephalitis is confirmed, aciclovir should be continued for at least 14 days. Upon stop, a repeat LP with PCR should confirm that CSF is negative for HSV. If still

positive, aciclovir should be continued for an additional week, with a new weekly LP until CSF is negative. For VZV, 10–15 mg/kg of aciclovir three times daily is recommended. In case of suspected vasculitis, steroids may be considered for this indication. Enterovirus encephalitis requires no specific treatment. Immunocompromised patients with CMV encephalitis should be treated with ganciclovir, although foscarnet or cidofovir are alternatives.

Other pathogens

Other causes of meningoencephalitis (mycobacteria, malaria, …) must be treated with appropriate anti-infective agents. When suspicion of a specific rare cause is strong, empirical therapy is defendable until the cause has been ruled out.

Healthcare-associated ventriculitis and meningitis

Pathogens associated with healthcare-associated meningitis and ventriculitis vary according to the clinical circumstances described above. After elective neurosurgery and TBI, common bacteria include staphylococci and gram-negative bacilli. In patients that underwent elective placement of neurosurgical devices such as CSF shunts, infections are usually caused by cutaneous organisms—*CNS* or *Propionibacterium acnes*. When determining probable etiologic pathogens and empirical therapy, the duration of hospitalization and local antimicrobial-susceptibility profiles prior to surgery should be considered, and multi-drug-resistant (MDR) bacteria might become a major problem. Empirical therapy should cover the most common pathogens implicated. In acute stroke or TBI patients with EVD-associated ventriculitis, the causative bacteria can be Gram positive or Gram negative [28, 29], and a recent single center study reported that 70.5% of cases were due to Gram-negative organisms with half of them isolating carbapenem-resistant *Acinetobacter (A.) baumannii* [58]. Empiric antibiotic therapy should be aimed at (methicillin resistant) *S. aureus (MRSA), coagulase-negative staphylococcus (CNS), Pseudomonas aeruginosa* and *A. baumannii.* Less common pathogens are enteric bacteria and *Candida* species. Empirical treatment of post-neurosurgical meningitis in patients at risk of *A. baumannii* infection should include high-dose intravenous meropenem with colistin in areas with high rates of resistance. The optimal duration of treatment of *A. baumannii* meningitis/ventriculitis is unknown, and experts recommend continuing antimicrobial therapy for 3 weeks [59].

The management of bacterial meningitis of ventriculitis in patients with EVDs should always involve removal and/or replacement of the indwelling device. EVDs are easy to remove. Internal ventricular catheters should be removed as well and replaced by a temporary EVD until cultures are negative for at least 7–10 days [54].

Intraventricular or intrathecal antibiotic treatment, with vancomycin, aminoglycosides, polymyxin B, or colistin, is sometimes considered, especially for difficult to eradicate surgical infections with MDR pathogens [60], such as *A. baumanii* [61], *Pseudomonas aeruginosa*, or *MRSA*, even when the exact indications of this therapy remain unknown. Adding intraventricular colistin in episodes caused by MDR *A. baumannii* is recommended, but intraventricular aminoglycosides can be an alternative if the strain is susceptible. Lower mortality associated with intrathecal colistin has been reported in patients with antibiotic-resistant *Acinetobacter* nosocomial meningitis [62].

Penetration of systemic antibiotics in the CSF is a particular concern, and several reports have been published to support therapeutic drug monitoring (TDM) in CSF for antimycobacterial [63] or antifungal agents [64], but also for more commonly used drugs where CSF penetration is known to be a problem, such as vancomycin [65] or ceftriaxone [66]. For vancomycin [67] and colistin [68], CSF TDM is often recommended, even for intrathecal administration.

Adjunctive treatments

Sepsis

The septic response to bacterial meningitis can be aggravated and is often fatal, especially in the classic Waterhouse–Friderichsen syndrome, where severe septic shock, diffuse intravascular coagulation, and adrenal infarctions are present. Sepsis management and the management of multiple organ failure (MOF) are not the scope of this review and should be done according to international guidelines [53]. When present, sepsis and MOF might be the main contributors to worse clinical outcomes and immediate fatality.

Intracranial hypertension

Elevated ICP is common after meningoencephalitis and is often lethal. Even while non-invasive assessment of ICP remains a challenge, and the predictive value of clinical or radiological signs to rule out intracranial hypertension is notoriously low [69], ICP monitoring in meningoencephalitis remains a subject of discussion. In analogy with traumatic brain injury [66], a tiered therapy for intracranial hypertension is usually proposed, including sedation, external ventricular drainage, hyperosmolar therapy with mannitol or hypertonic saline, and barbiturate coma or even surgical decompression for extreme cases. A prospective interventional trial of ICP specific therapy (mainly consisting of liquor drainage via an external ventricular drain, that was also used to measure

the ICP) suggested benefit over a historical control group where no routine early ICP-directed treatment was used [70]. Mainly due to the lack of prospective data, no recommendations can currently be made [71].

Temperature management

Antipyretics to control fever, even while frequently used in bacterial meningitis, had no demonstrated effect on outcome in two RCTs in children, performed in Angola [72] or Malawi [73]. Induced hypothermia is considered contraindicated in comatose bacterial meningitis patients, after a multicenter French RCT was stopped prematurely due to excess mortality in the hypothermia group [74].

Seizures

EEG must be systematically performed to rule out nonconvulsive seizures, in patients with proven or suspected meningitis/encephalitis that are comatose or have unexplained neurological deficits [24, 47]. In bacterial meningitis, risk factors for the development of seizures include pneumococcal etiology, and abnormalities on imaging studies, while the effect of older age is less consistent [75-77]. The role of prophylactic antiseizure treatment is not well established, and has not made it into the guidelines [24]. For viral encephalitis, in the absence of adequately powered RCTs, the evidence for routine anti-epileptics for the primary or secondary prevention of seizures remains equally weak [78]. Rather, it is advisable to have a low threshold for starting antiseizure therapy in patients with meningitis or encephalitis, where a clinical suspicion or a high risk for seizures exists [76].

Glycerol

Studies on the role of oral glycerol to prevent neurological complications of bacterial meningitis have demonstrated conflicting results. A multicenter double-blind RCT found an effect of oral glycerol in monotherapy and combined with dexamethasone, in reducing neurological complications [79]. However, a subsequent trial in adult meningitis patients in Malawi [80], a resource-poor setting with a high HIV prevalence, was stopped prematurely due to excess mortality in the glycerol group. Another study in children in Malawi [73] found no effect on outcome.

Conclusion

Meningitis and encephalitis represent severe and underrecognized causes of brain injury and mortality in the ICU setting. The incidence of healthcare-associated meningitis and ventriculitis is increasing, and requires special consideration. Admission to an intensive care unit (ICU) is often necessary, to prevent or treat associated systemic and neurological complications. Recent advances in molecular biology allow for faster and more accurate etiological diagnosis. Further studies in ICU patients focusing on management of raised intracranial pressure, seizure detection, and treatment and potential adjunctive therapies to improve neurologic outcomes are urgently needed.

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Compliance with ethical standards

Conflicts of interest

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Ethical approval

This article does not contain any studies involving animals or human participants performed by any of the authors. The review, and decisions on authorship, were performed in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

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References

1. Vincent J, Marshall J, Anzueto A et al (2009) International study of the prevalence and outcomes of infection in intensive care units. JAMA J Am Med Assoc 302:2323–2329
2. Zunt JR, Kassebaum NJ, Blake N et al (2018) Global, regional, and national burden of meningitis, 1990–2016: a systematic analysis for the global burden of disease study 2016. Lancet Neurol 17:1061–1082. https://doi.org/10.1016/S1474-4422(18)30387-9
3. McGill F, Heyderman RS, Panagiotou S et al (2016) Acute bacterial meningitis in adults. Lancet 388:3036–3047. https://doi.org/10.1016/S0140-6736(16)30654-7
4. van de Beek D, Cabellos C, Dzupova O et al (2016) ESCMID guideline: diagnosis and treatment of acute bacterial meningitis. Clin Microbiol Infect 22:S37–S62. https://doi.org/10.1016/j.cmi.2016.01.007
5. Charlier C, Perrodeau É, Leclercq A et al (2017) Clinical features and prognostic factors of listeriosis: the MONALISA national prospective cohort study. Lancet Infect Dis 17:510–519. https://doi.org/10.1016/S1473-3099(16)30521-7
6. Brouwer MC, Wijdicks EFM, van de Beek D (2016) What's new in bacterial meningitis. Intensive Care Med 42:415–417. https://doi.org/10.1007/s00134-015-4057-x

7. Bijlsma MW, Brouwer MC, Spanjaard L et al (2014) A decade of herd protection after introduction of meningococcal serogroup C conjugate vaccination. Clin Infect Dis 59:1216–1221. https://doi.org/10.1093/cid/ciu601
8. Bijlsma MW, Brouwer MC, Kasanmoentalib ES et al (2016) Community-acquired bacterial meningitis in adults in the Netherlands, 2006–14: a prospective cohort study. Lancet Infect Dis 16:339–347. https://doi.org/10.1016/S1473-3099(15)00430-2
9. Parikh SR, Andrews NJ, Beebeejaun K et al (2016) Effectiveness and impact of a reduced infant schedule of 4CMenB vaccine against group B meningococcal disease in England: a national observational cohort study. Lancet 388:2775–2782. https://doi.org/10.1016/S0140-6736(16)31921-3
10. Bonten MJM, Huijts SM, Bolkenbaas M et al (2015) Polysaccharide conjugate vaccine against pneumococcal pneumonia in adults. N Engl J Med 372:1114–1125. https://doi.org/10.1056/NEJMoa1408544
11. Weinberger DM, Malley R, Lipsitch M (2011) Serotype replacement in disease after pneumococcal vaccination. Lancet 378:1962–1973. https://doi.org/10.1016/S0140-6736(10)62225-8
12. Waight PA, Andrews NJ, Ladhani SN et al (2015) Effect of the 13-valent pneumococcal conjugate vaccine on invasive pneumococcal disease in England and Wales 4 years after its introduction: an observational cohort study. Lancet Infect Dis 15:535–543. https://doi.org/10.1016/S1473-3099(15)70044-7
13. Hoogman M, Van De Beek D, Weisfelt M et al (2007) Cognitive outcome in adults after bacterial meningitis. J Neurol Neurosurg Psychiatry 78:1092–1096. https://doi.org/10.1136/jnnp.2006.110023
14. Auburtin M, Wolff M, Charpentier J et al (2006) Detrimental role of delayed antibiotic administration and penicillin-nonsusceptible strains in adult intensive care unit patients with pneumococcal meningitis: The PNEUMOREA prospective multicenter study. Crit Care Med 34:2758–2765. https://doi.org/10.1097/01.CCM.0000239434.26669.65
15. Venkatesan A, Tunkel AR, Bloch KC et al (2013) Case definitions, diagnostic algorithms, and priorities in encephalitis: consensus statement of the international encephalitis consortium. Clin Infect Dis 57:1114–1128. https://doi.org/10.1093/cid/cit458
16. Granerod J, Ambrose HE, Davies NWS et al (2010) Causes of encephalitis and differences in their clinical presentations in England: a multicentre, population-based prospective study. Lancet Infect Dis 10:835–844. https://doi.org/10.1016/S1473-3099(10)70222-X
17. Da Silva IRF, Frontera JA, De Filippis AMB, >Do Nascimento OJM (2017) Neurologic complications associated with the Zika virus in Brazilian adults. JAMA Neurol 74:1190–1198. https://doi.org/10.1001/jamaneurol.2017.1703
18. Jaquet P, De Montmollin E, Dupuis C et al (2019) Functional outcomes in adult patients with herpes simplex encephalitis admitted to the ICU: a multicenter cohort study. Intensive Care Med 45:1103–1111. https://doi.org/10.1007/s00134-019-05684-0
19. Tan IL, McArthur JC, Venkatesan A, Nath A (2012) Atypical manifestations and poor outcome of herpes simplex encephalitis in the immunocompromised. Neurology 79:2125–2132. https://doi.org/10.1212/WNL.0b013e3182752ceb
20. Swinnen B, Saegeman V, Beuselinck K et al (2019) Predictive value of JC virus PCR in cerebrospinal fluid in the diagnosis of PML. Diagn Microbiol Infect Dis 95(3):114859. https://doi.org/10.1016/j.diagmicrobio.2019.06.011
21. Sonneville R, Venkatesan A, Honnorat J (2019) Understanding autoimmune encephalitis in the ICU. Intensive Care Med. https://doi.org/10.1007/s00134-019-05773-0
22. Tsai M-H, Lu C-H, Huang C-R et al (2006) Infection bacterial meningitis in young adults in Southern Taiwan: clinical characteristics and therapeutic outcomes. Infection. https://doi.org/10.1007/s15010-006-4144-6
23. Castelblanco RL, Lee MJ, Hasbun R (2014) Epidemiology of bacterial meningitis in the USA from 1997 to 2010: a population-based observational study. Lancet Infect Dis 14:813–819. https://doi.org/10.1016/S1473-3099(14)70805-9
24. Tunkel AR, Hasbun R, Bhimraj A et al (2017) 2017 Infectious diseases society of America's clinical practice guidelines for healthcare-associated ventriculitis and meningitis. Clin Infect Dis 64:e34–e65. https://doi.org/10.1093/cid/ciw861
25. McClelland S, Guo H, Okuyemi KS (2011) Population-based analysis of morbidity and mortality following surgery for intractable temporal lobe epilepsy in the United States. Arch Neurol 68:725–729. https://doi.org/10.1001/archneurol.2011.7
26. Kourbeti IS, Vakis AF, Ziakas P et al (2015) Infections in patients undergoing craniotomy: risk factors associated with post-craniotomy meningitis. J Neurosurg 122:1113–1119. https://doi.org/10.3171/2014.8.JNS132557
27. Lozier AP, Sciacca RR, Romagnoli MF, Connolly ES (2002) Ventriculostomy-related infections: a critical review of the literature. Neurosurgery 51:170–182. https://doi.org/10.1227/01.NEU.0000017465.78245.6C
28. Citerio G, Signorini L, Bronco A et al (2015) External ventricular and lumbar drain device infections in icu patients: a prospective multicenter Italian study. Crit Care Med 43:1630–1637. https://doi.org/10.1097/CCM.0000000000001019
29. Ramanan M, Lipman J, Shorr A, Shankar A (2015) A meta-analysis of ventriculostomy-associated cerebrospinal fluid infections. BMC Infect Dis 14:1–12. https://doi.org/10.1186/s12879-014-0712-z
30. Jakobs M, Klein S, Eigenbrod T et al (2019) The siludrain trial: a prospective randomized controlled trial comparing standard versus silver-impregnated lumbar drains. J Neurosurg 1306:2040–2047. https://doi.org/10.3171/2018.1.JNS181522
31. Conen A, Walti LN, Merlo A et al (2008) Characteristics and treatment outcome of cerebrospinal fluid shunt-associated infections in adults: a retrospective analysis over an 11-year period. Clin Infect Dis 47:73–82. https://doi.org/10.1086/588298
32. Van De Beek D, De Gans J, Spanjaard L et al (2004) Clinical features and prognostic factors in adults with bacterial meningitis. N Engl J Med 351:1849–1859. https://doi.org/10.1056/NEJMoa040845
33. Thomas KE, Hasbun R, Jekel J, Quagliarello VJ (2002) The diagnostic accuracy of Kernig's sign, Brudzinski's sign, and nuchal rigidity in adults with suspected meningitis. Clin Infect Dis 35:46–52. https://doi.org/10.1086/340979
34. Penido Nde O, Borin A, Iha LC et al (2005) Intracranial complications of otitis media: 15 years of experience in 33 patients. Otolaryngol Head Neck Surg 132(1):37–42. https://doi.org/10.1016/j.otohns.2004.08.007
35. Sonneville R, Magalhaes E, Meyfroidt G (2017) Central nervous system infections in immunocompromised patients. Curr Opin Crit Care 23:128–133. https://doi.org/10.1097/MCC.0000000000000397
36. van de Beek D, de Gans J, Tunkel AR, Wijdicks EFM (2006) Community-acquired bacterial meningitis in adults. N Engl J Med 354:44–53. https://doi.org/10.1136/jnnp.2007.139725
37. Stahl JP, Azouvi P, Bruneel F et al (2017) Guidelines on the management of infectious encephalitis in adults. Med Mal Infect 47:179–194. https://doi.org/10.1016/j.medmal.2017.01.005
38. Tyler KL (2018) Acute viral encephalitis. N Engl J Med 379:557–566. https://doi.org/10.1056/NEJMra1708714
39. Sonneville R, Demeret S, Klein I et al (2008) Acute disseminated encephalomyelitis in the intensive care unit: clinical features and outcome of 20 adults. Intensive Care Med 34:528–532. https://doi.org/10.1007/s00134-007-0926-2
40. Graus F, Cellucci T, Cortese I et al (2016) A clinical approach to diagnosis of autoimmune encephalitis. Lancet Neurol 15:391–404. https://doi.org/10.1016/S1474-4422(15)00401-9.A
41. Cantier M, Morisot A, Guérot E et al (2018) Functional outcomes in adults with tuberculous meningitis admitted to the ICU: a multicenter cohort study. Crit Care 22:1–8. https://doi.org/10.1186/s13054-018-2140-8
42. Leber A, Everhart K, Demogines A et al (2015) Multi-center clinical evaluation of a multiplex meningitis / encephalitis pcr panel for simultaneous detection of bacteria, yeast, and viruses in cerebrospinal fluid specimens. J Clin Microbiol 54:2251–2261. https://doi.org/10.1128/JCM.00730-16.Editor
43. Brouwer MC, Tunkel AR, Van De Beek D (2010) Epidemiology, diagnosis, and antimicrobial treatment of acute bacterial meningitis. Clin Microbiol Rev 23:467–492. https://doi.org/10.1128/CMR.00070-09
44. Wilson MR, Sample HA, Zorn KC et al (2019) Clinical metagenomic sequencing for diagnosis of meningitis and encephalitis. N Engl J Med 380:2327–2340. https://doi.org/10.1056/NEJMoa1803396
45. Weisfelt M, Van De Beek D, Spanjaard L et al (2006) Clinical features, complications, and outcome in adults with pneumococcal meningitis: a prospective case series. Lancet Neurol 5:123–129. https://doi.org/10.1016/S1474-4422(05)70288-X

46. Chow FC, Glaser CA, Sheriff H et al (2015) Use of clinical and neuroimaging characteristics to distinguish temporal lobe herpes simplex encephalitis from its mimics. Clin Infect Dis 60:1377–1383. https://doi.org/10.1093/cid/civ051
47. Sutter R, Kaplan PW, Cervenka MC et al (2015) Electroencephalography for diagnosis and prognosis of acute encephalitis. Clin Neurophysiol 126:1524–1531. https://doi.org/10.1016/j.clinph.2014.11.006
48. Bodilsen J, Dalager-Pedersen M, Schønheyder HC, Nielsen H (2016) Time to antibiotic therapy and outcome in bacterial meningitis: a Danish population-based cohort study. BMC Infect Dis. https://doi.org/10.1186/s12879-016-1711-z
49. Bretonnière C, Jozwiak M, Girault C et al (2015) Rifampin use in acute community-acquired meningitis in intensive care units: the French retrospective cohort ACAM-ICU study. Crit Care 19:1–9. https://doi.org/10.1186/s13054-015-1021-7
50. Bouadma L, Schortgen F, Thomas R et al (2006) Adults with spontaneous aerobic Gram-negative bacillary meningitis admitted to the intensive care unit. Clin Microbiol Infect 12:287–290. https://doi.org/10.1111/j.1469-0691.2005.01346.x
51. Teckie G, Karstaedt A (2015) Spontaneous adult Gram-negative bacillary meningitis in Soweto, South Africa. Int J Infect Dis 30:e38–e40. https://doi.org/10.1016/j.ijid.2014.10.006
52. Bodilsen J, Brouwer MC, Kjærgaard N et al (2018) Community-acquired meningitis in adults caused by *Escherichia coli* in Denmark and The Netherlands. J Infect. https://doi.org/10.1016/j.jinf.2018.05.009
53. Rhodes A, Evans LE, Alhazzani W et al (2017) Surviving sepsis campaign: international guidelines for management of sepsis and septic shock: 2016. Intensive Care Med 43:304–377. https://doi.org/10.1007/s00134-017-4683-6
54. van de Beek D, Drake JM, Tunkel AR (2010) Nosocomial Bacterial Meningitis. N Engl J Med 362:146–154. https://doi.org/10.1056/NEJMra0804573
55. Brouwer MC, Mcintyre P, Prasad K, van de Beek D (2015) Corticosteroids for acute bacterial meningitis. Cochrane Database Syst Rev. https://doi.org/10.1002/14651858.CD004405.pub5
56. Gallegos C, Tobolowsky F, Nigo M, Hasbun R (2018) Delayed cerebral injury in adults with bacterial meningitis. Crit Care Med 46:e811–e814. https://doi.org/10.1097/ccm.0000000000003220
57. Solomon T, Michael BD, Smith PE et al (2012) Management of suspected viral encephalitis in adults—association of British neurologists and British infection association national guidelines. J Infect 64:347–373. https://doi.org/10.1016/j.jinf.2011.11.014
58. Hussein K, Rabino G, Feder O et al (2019) Risk factors for meningitis in neurosurgical patients with cerebrospinal fluid drains: prospective observational cohort study. Acta Neurochir (Wien) 161:517–524. https://doi.org/10.1007/s00701-019-03801-y
59. Garnacho-Montero J, Dimopoulos G, Poulakou G et al (2015) *baumannii* infections in the ICU. Intensive Care Med 41:2057–2075
60. Falagas ME, Bliziotis IA (2007) Pandrug-resistant Gram-negative bacteria: the dawn of the post-antibiotic era? Int J Antimicrob Agents 29:630–636. https://doi.org/10.1016/j.ijantimicag.2006.12.012
61. Katragkou A, Roilides E (2005) *baumannii* central nervous system infections with colistin [2]. J Clin Microbiol 43:4916–4917. https://doi.org/10.1128/JCM.43.9.4916-4917.2005
62. Kim BN, Peleg AY, Lodise TP et al (2009) Management of meningitis due to antibiotic-resistant *Acinetobacter species*. Lancet Infect Dis 9:245–255. https://doi.org/10.1016/S1473-3099(09)70055-6
63. Motta I, Calcagno A, Bonora S (2018) Pharmacokinetics and pharmacogenetics of anti-tubercular drugs: a tool for treatment optimization? Expert Opin Drug Metab Toxicol 14:59–82. https://doi.org/10.1080/17425255.2018.1416093
64. Nierenberg NE, Thompson GR, Lewis JS et al (2010) Voriconazole use and pharmacokinetics in combination with interferon-γ for refractory cryptococcal meningitis in a patient receiving low-dose ritonavir. Med Mycol 48:532–536. https://doi.org/10.3109/13693780903325282
65. Beach JE, Perrott J, Turgeon RD, Ensom MHH (2017) Penetration of vancomycin into the cerebrospinal fluid: a systematic review. Clin Pharmacokinet 56:1479–1490. https://doi.org/10.1007/s40262-017-0548-y
66. Le Turnier P, Navas D, Garot D et al (2019) Tolerability of high-dose ceftriaxone in CNS infections: a prospective multicentre cohort study. J Antimicrob Chemother 74:1078–1085. https://doi.org/10.1093/jac/dky553
67. Ng K, Mabasa VH, Chow I, Ensom MHH (2014) Systematic review of efficacy, pharmacokinetics, and administration of intraventricular vancomycin in adults. Neurocrit Care 20:158–171. https://doi.org/10.1007/s12028-012-9784-z
68. Tafelski S, Wagner L, Angermair S, Deja M (2017) Therapeutic drug monitoring for colistin therapy in severe multi-resistant Acinetobacter intracerebral abscess: a single case study with high-dose colistin and review of literature. SAGE Open Med Case Rep 5:2050313X1771163. https://doi.org/10.1177/2050313x17711630
69. Fernando S, Tran A, Cheng W et al (2019) Diagnosis of elevated intracranial pressure in critically ill adults—a systematic review and meta-analysis. BMJ 366:1–10. https://doi.org/10.1017/cem.2019.142
70. Glimåker M, Johansson B, Halldorsdottir H et al (2014) Neuro-intensive treatment targeting intracranial hypertension improves outcome in severe bacterial meningitis: an intervention-control study. PLoS ONE ONE 9:e91976. https://doi.org/10.1371/journal.pone.0091976
71. Tariq A, Aguilar-Salinas P, Hanel RA et al (2017) The role of ICP monitoring in meningitis. Neurosurg Focus 43:1–7. https://doi.org/10.3171/2017.8.FOCUS17419
72. Pelkonen T, Roine I, Cruzeiro ML et al (2011) Slow initial β-lactam infusion and oral paracetamol to treat childhood bacterial meningitis: a randomised, controlled trial. Lancet Infect Dis 11:613–621. https://doi.org/10.1016/S1473-3099(11)70055-X
73. Molyneux EM, Kawaza K, Phiri A et al (2014) Glycerol and acetaminophen as adjuvant therapy did not affect the outcome of bacterial meningitis in malawian children. Pediatr Infect Dis J 33:214–216. https://doi.org/10.1097/INF.0000000000000122
74. Mourvillier B, Tubach F, Van De Beek D et al (2013) Induced hypothermia in severe bacterial meningitis: a randomized clinical trial. JAMA J Am Med Assoc 310:2174–2183. https://doi.org/10.1001/jama.2013.280506
75. Cabellos C, Verdaguer R, Olmo M et al (2009) Community-acquired bacterial meningitis in elderly patients: experience over 30 years. Medicine (Baltimore) 88:115–119. https://doi.org/10.1097/MD.0b013e31819d50ef
76. Zoons E, Weisfelt M, de Gans J et al (2008) Seizures in adults with bacterial meningitis. Neurology 70:2109–2115. https://doi.org/10.1212/01.wnl.0000288178.91614.5d
77. Larsen FTBD, Brandt CT, Larsen L et al (2019) Risk factors and prognosis of seizures in adults with community-acquired bacterial meningitis in Denmark: Observational cohort studies. BMJ Open 9:1–9. https://doi.org/10.1136/bmjopen-2019-030263
78. Pandey S, Rathore C, Michael BD (2016) Antiepileptic drugs for the primary and secondary prevention of seizures in viral encephalitis. Cochrane Database Syst Rev. https://doi.org/10.1002/14651858.CD010247.pub3
79. Peltola H, Roine I, Fernandez J et al (2007) Adjuvant glycerol and/or dexamethasone to improve the outcomes of childhood bacterial meningitis: a prospective, randomized, double-blind, placebo-controlled trial. Clin Infect Dis 45:1277–1286. https://doi.org/10.1086/522534
80. Ajdukiewicz KMB, Cartwright KE, Scarborough M et al (2011) Glycerol adjuvant therapy in adults with bacterial meningitis in a high HIV seroprevalence setting in Malawi: a double-blind, randomised controlled trial. Lancet Infect Dis 11:293–300. https://doi.org/10.1016/S1473-3099(10)70317-0